Remarks

Claims 36-54 are pending in the subject application. By this Amendment, Applicants have amended claims 36 and 53. Support for the amendments can be found throughout the subject specification and in the claims as originally filed (see, for example, the paragraph bridging pages 5-6 and paragraph 1, page 6). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 36-55 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 36-54 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a phosphoantigen that activates gamma delta T cells to said mammal. The Office Action indicates the arguments and declaratory evidence previously submitted has been considered and has not been found persuasive. Specifically, the Office Action argues that:

> those skilled in the art could not extrapolate the disclosure of the specification into a method to reduce airway hyperresponsiveness in a mammal by administering any phosphoantigen. The La Place declaration which demonstrates the administration of one non-disclosed proprietary phosphoantigen "compound X" to treat hyperresponsiveness is not sufficient to establish that the genus of all phophoantigen compounds could be used to reduce airway hyperresponsivesness in a mammal that has or is at risk of developing a respiratory condition associated with airway hyperresponsiveness to overcome the instant rejection. The art shows that "both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation" of γδ T cells. (In particular, Burk et al., PTO-892 mailed 11/21/2007, Reference D, abstract, whole document). In addition, the 2006 post-filing date art of Zhang et al. teaches that the structure of well-known, previously reported phosphoantigens is not correct (PTO-892, Reference D; In particular, whole document). On page 985, Zhang et al. teaches that "There are, however, many questions as to the mechanism of action of phosphoantigens, as well as to their chemical structures." The art of Zhang et al. combined with the art of Burk et al. teaches that those of ordinary skill in the art do not know what phosphoantigen structures correlate with in vitro gamma delta T cell activation, much less in vivo gamma delta T cell activation that increases TNF-alpha and leads to reduced airway hyperresponsiveness. Neither the specification nor the state of the art at the time of invention provides adequate guidance and support regarding which phosphoantigens can be used in the reduce airway hyperresponsiveness to enable the instant claims.

> Therefore, those skilled in the art at the time of the invention would not know to use IPP or any phophoantigen in general to perform the recited method.

At the outset, Applicants wish to clarify that phosphoantigens have not been asserted as the means by which airway hyperresponsiveness can be reduced. Rather, and as noted in the as-filed specification in the paragraph bridging pages 28-29:

> ... the method of the present invention includes the use of a variety of agents (i.e., regulatory compounds) which, by acting on γδ T cells, increase the proliferation, activation/biological activity, and/or survival of γδ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory γδ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal. Such agents are generally referred to herein as γδ T cell agonists. According to the present invention, a γδ T cell agonist is any agent which increases, typically by direct action on the cell, the proliferation, activation/biological activity, and/or survival of γδ T cells, and includes agents which act directly on the γδ T cell receptor. A γδ T cell agonist, as referred to herein, can further include, for example, compounds that are products of rational drug design, natural products, and compounds having partially or fully defined γδ T cell stimulatory properties. A γδ T cell agonist can be a protein-based compound, a carbohydrate-based compound, a lipid-based compound, a nucleic acid-based compound, a natural organic compound, a synthetically derived organic compound, an antibody, or fragments thereof. A variety of known γδ T cell agonists are described below and all are encompassed by the present invention.

In this context, Applicants respectfully submit that it is the activation (by a γδ T-cell agonist) and activity of γδ T-cells that mediates a reduction in airway hyperresponsiveness. As noted in the as-filed specification at page 36, paragraph 2, phosphoantigens are but one example of agonists useful in this therapeutic context. Applicants also note that the as-filed specification provides ample teaching as to how one skilled in the art could screen phosphoantigens for the desired activity (see, for example, the paragraph bridging pages 52-53).

Turning to the reasons given for maintaining the rejection of record, Applicants respectfully submit that the references cited in support of the enablement rejection do not support a finding that the claimed invention is not enabled. For example, Zhang *et al.* specifically states that various phosphoantigen compounds were assessed for biological activity on γδ T-cells (*e.g.*, the ability to stimulate TNF-α production and proliferation; see page 988, column 2). As noted in that passage "In both the TNF-α release and cell proliferation assays, **we find the expected activity pattern** for the positive controls ..." (page 988, column 2, lines 9-12; emphasis added). Thus, it is clear that those

skilled in the art expected the treatment of γδ T-cells with various phosphoantigens to result in the stimulation of both cell proliferation and TNF-α production.

While Burk *et al.*, published in 1995, specifically indicates that "both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation" of γδ T cells, Applicants respectfully submit that the reference serves to provide guidance to those skilled in the art as to those structural requirements for phosphoantigens necessary to provide agonistic activity for γδ T-cells. Applicants also note that a large number of non-nucleotidic phosphoantigens were known to those skilled in the art prior to, or around, the effective filing date of the instant application. For example, Espinosa *et al.* (Microbes and Infection, 2001, 3:645-654) provide a table of phosphoantigens known to stimulate the proliferation of γδ T-cells (see Table 1, page 648).

While Applicants are cognizant that post-filing date references cannot be used to demonstrate that the as-filed specification is enabling, one exception to this rule allows for the use of such a reference if it provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *See In re Hogan, 559 F.2d 595, 605, 194 U.S.P.Q. 527, 537 (C.C.P.A. 1977).* In this regard, Applicants note that Espinosa *et al.* discuss a number of natural and synthetic phosphoantigens that were known to those skilled in the art prior to, or around, the earliest effective filing date of this application (see pages 646-648, the references cited in this passage and Table 1). With respect to the various phosphoantigens referred to in Table 1, Applicants note that references 38, 41, 42, 44 and 81 were published between 1992 and 1997, reference 83 was published in 1999 and reference 82 was published in 2000. Thus, the vast majority of the phosphoantigens discussed in Table 1, and the passage referred to above (pages 636-648), were known to those skilled in the art prior to the effective filing date of the instant application (September 30, 1999). Accordingly, it is respectfully submitted that one skilled in the art would have known how to make and use the claimed invention and reconsideration and withdrawal of the rejection of record is respectfully requested.

Claims 36-54 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office Action argues that "the specification has not adequately described a correlation between function (reduces airway hyperresponsiveness) and phosphoantigen structure responsible for reducing airway hyperresponsiveness such that one of ordinary skill in the art would have known which phosphoantigens could be used to generate the disclosed function of reducing airway hyperresponsiveness in a mammal." The Office Action also argues that the specification does not adequately describe the genus of all phosphoantigen non-peptide compounds for use in the claimed invention and that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features and that without a correlation between structure and function, the claims do little more than define the claimed invention by function. Finally, the Office Action argues that one of ordinary skill in the art would not be able to determine which phosphoantigens would work in the claimed invention since neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus of phosphoantigens that would work to reduce airway hyperresponsiveness in the claimed invention (citing in support of this proposition Burk *et al.* and Zhang *et al.*).

In this regard, Applicants, again, note, that phosphoantigens are utilized to activate/stimulate proliferation of γδ T-cells and that the T-cells are responsible for mediating a reduction in airway hyperresponsiveness. Thus, and it is respectfully submitted that arguments pertaining to the "correlation between function (reduces airway hyperresponsiveness) and phosphoantigen structure responsible for reducing airway hyperresponsiveness such that one of ordinary skill in the art would have known which phosphoantigens could be used to generate the disclosed function of reducing airway hyperresponsiveness in a mammal" are not germane to whether the claimed invention satisfies the written description requirement.

The Office Action cites to Burk *et al.* and Zhang *et al.* in an effort to support its finding that the as-filed specification fails to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In this regard, the Office Action argues that Zhang *et al.* combined with the art of Burk *et al.* teaches that those of ordinary

skill in the art do not know what phosphoantigen structures correlate with *in vitro* gamma delta T cell activation, much less *in vivo* gamma delta T cell activation that increases TNF-alpha and leads to reduced airway hyperresponsiveness.

Contrary to the assertion made in the Office Action, structure-activity (structure/function) studies have been carried out on a number of synthetic phosphoantigens (see Espinosa *et al.*, page 647, column 2, "3. Synthetic phosphoantigen agonists"). As noted in that passage, "dozens of phosphorylated compounds have been chemically synthesized and assayed of on γδ T-cells to determine their structure-activity relationships" (page 647, column 2, "3. Synthetic phosphoantigen agonists") and the majority of the publications referred to in that passage were published prior to the earliest effective filing date of the claimed invention. Applicants also respectfully submit that phosphoantigens suitable for both *in vitro* and *in vivo* activation of γδ T-cells were known to those skilled in the art prior to the earliest effective date of the claimed invention (see, for example, Espinosa *et al.*, page 648, Table 1). As noted in the previous response, compliance with the written description requirement is assessed from the viewpoint of one skilled in the art, taking into account subject matter known in the field of invention (*see S3, Inc. v. Nvidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001)) and there is no requirement for the re-description of that which is known to those skilled in the art (*see Capon v. Eshhar,* 418 F.3d 1349,1359-60 (Fed. Cir. 2005) and *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006)). Accordingly, it is respectfully submitted that the as-filed specification and claimed invention comply with the written description requirements and reconsideration and withdrawal of this rejection is respectfully requested.

Claims 36-54 are rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1, 2, 4, 18, 19, 23-33, 36, 38 and 39 of U.S. Patent No. 6,737,398. Applicants respectfully submit that the claims are not obvious over the cited patent. However, in an effort to expedite prosecution in this matter a terminal disclaimer is being filed herewith. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants

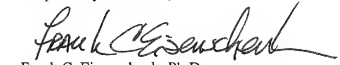
expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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